

# Update on Alzheimer's Disease Prevention Trials

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Eli Lilly, Avid, Janssen

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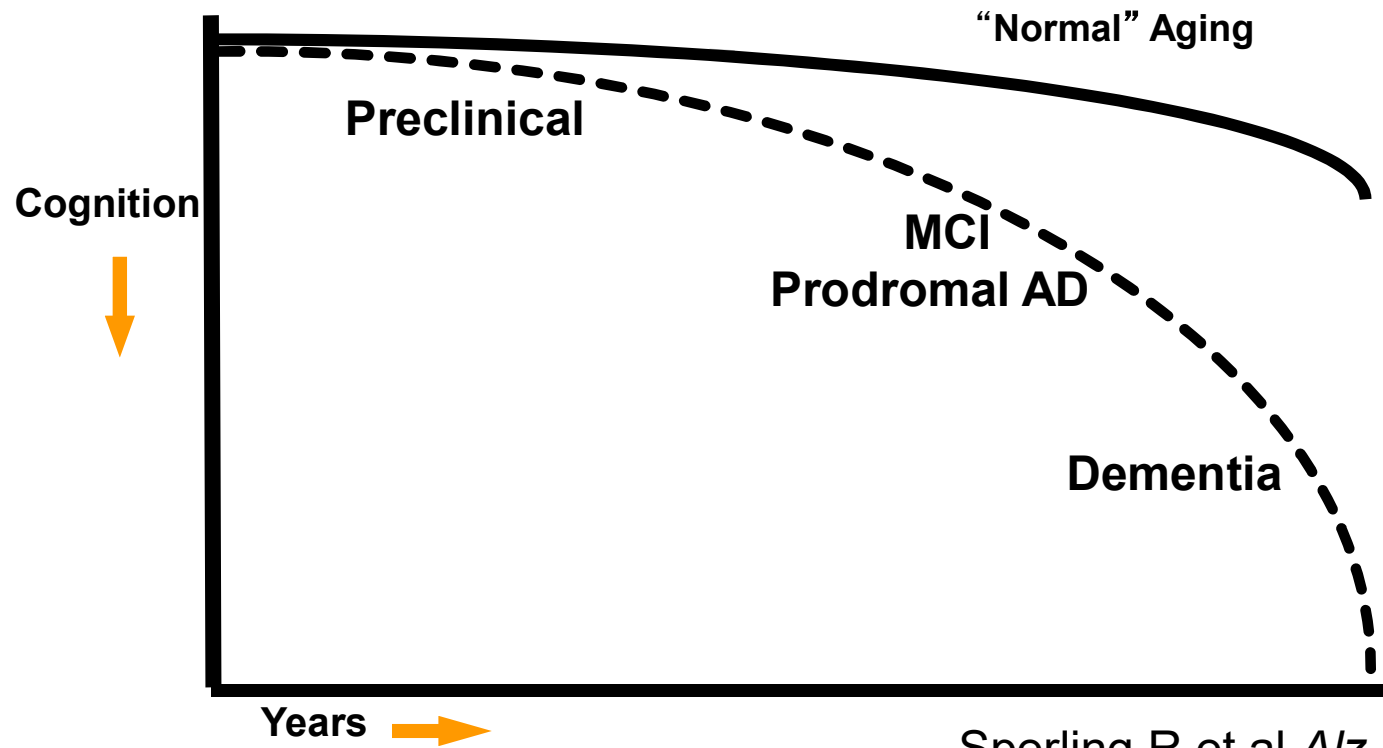
Alzheimer's Association

Fidelity Biosciences, GHR Foundation, Gates Ventures

Eli Lilly, Janssen

Accelerating Medicines Partnership FNIH

# The continuum of Alzheimer's disease

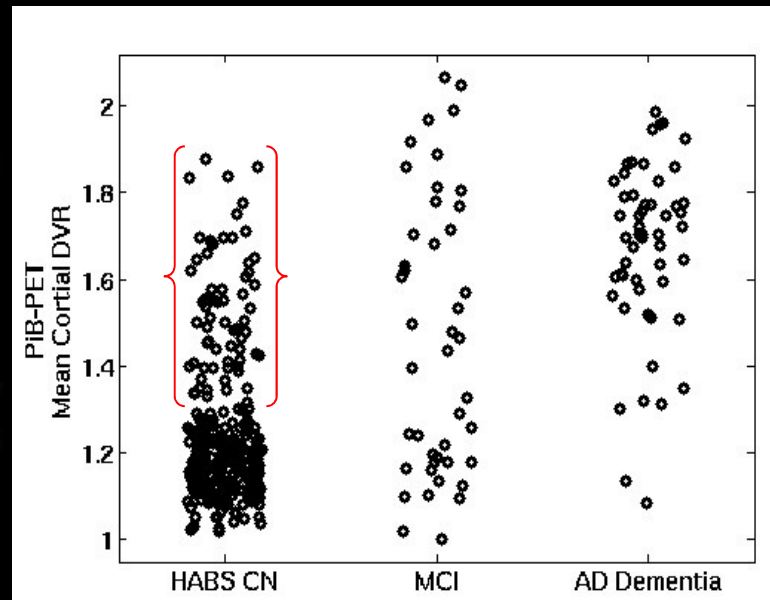
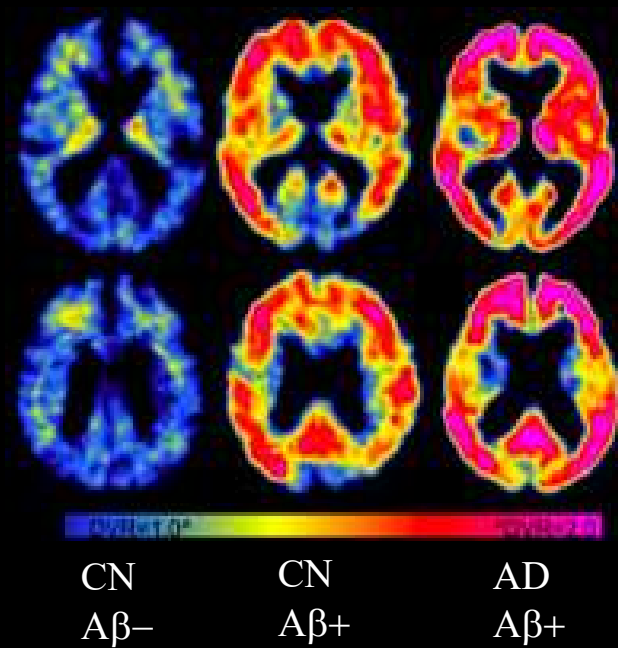


Sperling R et al *Alz & Dem* 2011  
NIA-AA Preclinical Workgroup

## Case for Earlier Intervention

- Twelve Phase 3 Trial Failures at the stage of mild-moderate AD dementia over past decade
  - Too Little? Underdosing – particularly antibodies
  - Too Late? Widespread neurodegeneration entrenched - Signals of efficacy in mildest groups?
- Delaying dementia by 5 years would reduce projected Medicare costs by nearly 50%
- Think about what happens in cancer, stroke, HIV, diabetes, osteoporosis .... if we wait to treat until after symptoms appear?

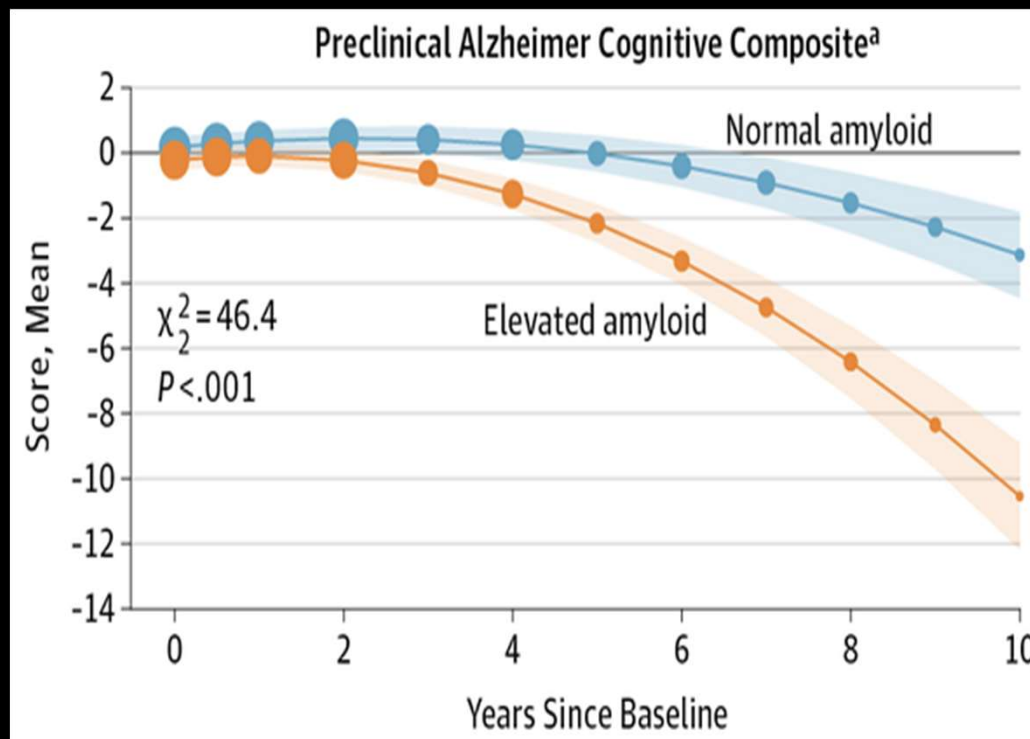
# PET Amyloid Imaging Across the Spectrum of AD



Harvard Aging Brain Study

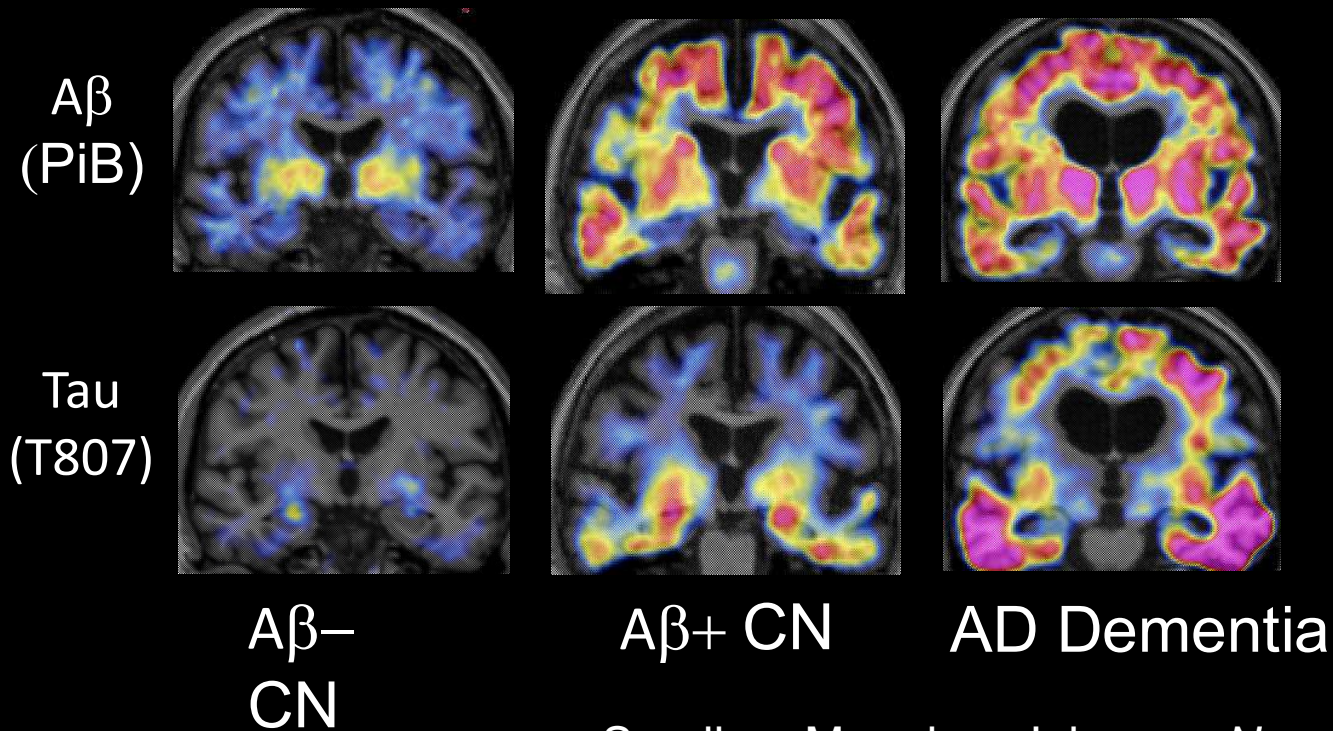
Sperling, Mormino, Johnson *Neuron* 2014

# Preclinical Alzheimer Cognitive Composite (PACC) in ADNI



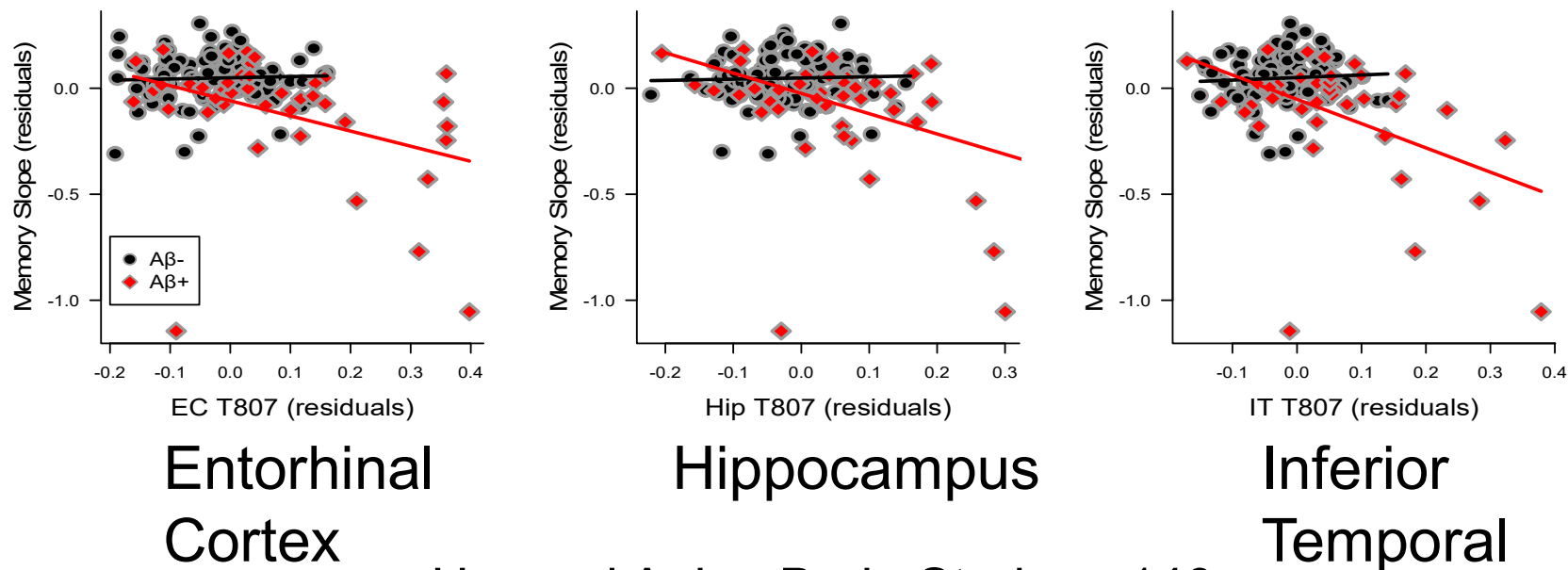
Donohue M., Sperling R et al. *JAMA*  
2017

# Amyloid and Tau PET Imaging



Sperling, Mormino, Johnson *Neuron* 2014

# Prospective Longitudinal Memory Decline related to Tau in Amyloid+ Normals

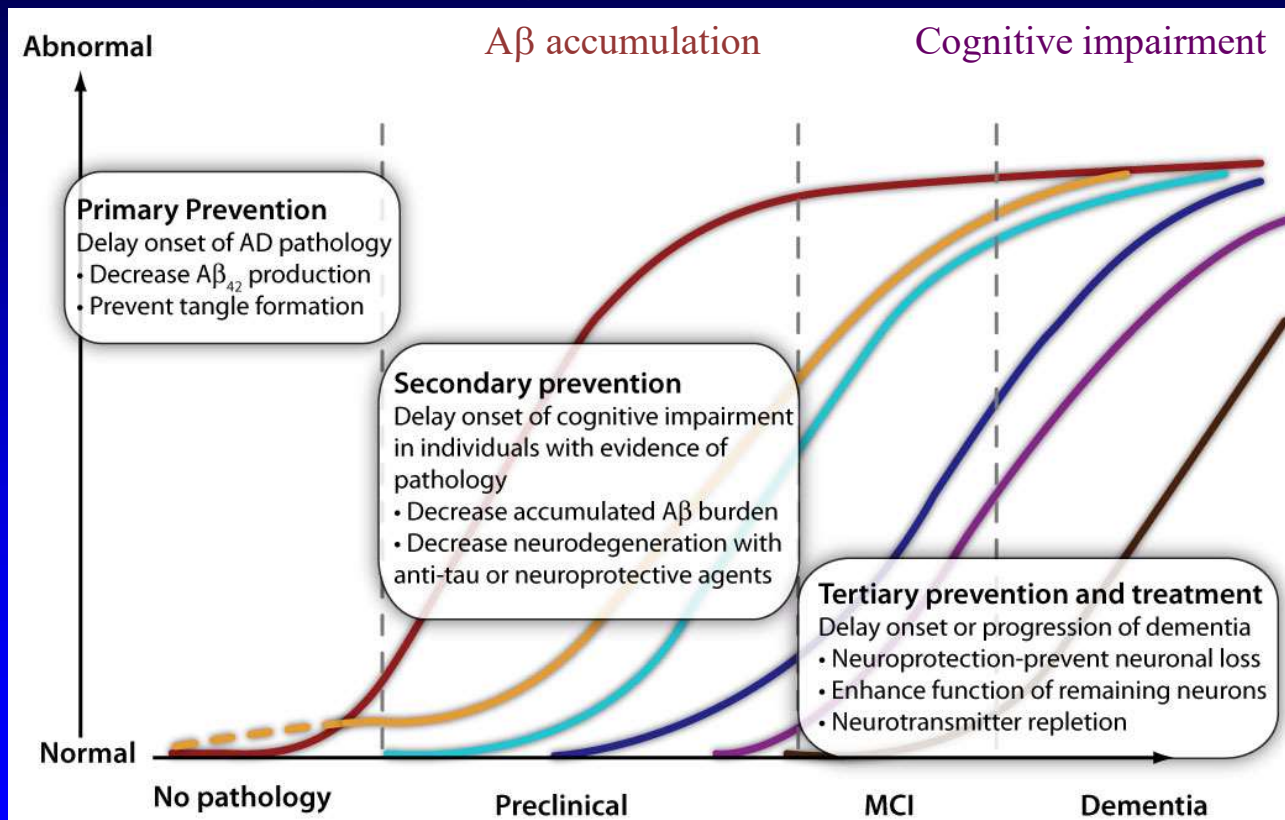


Harvard Aging Brain Study n=140  
Mean follow-up 2.01+/- .77 years

Sperling, Mormino et al *Annals of Neurology* 2019



# Testing the Right Target and Right Drug at the Right Stage of Alzheimer's Disease



Sperling, Jack, Aisen *Science Translational Medicine*

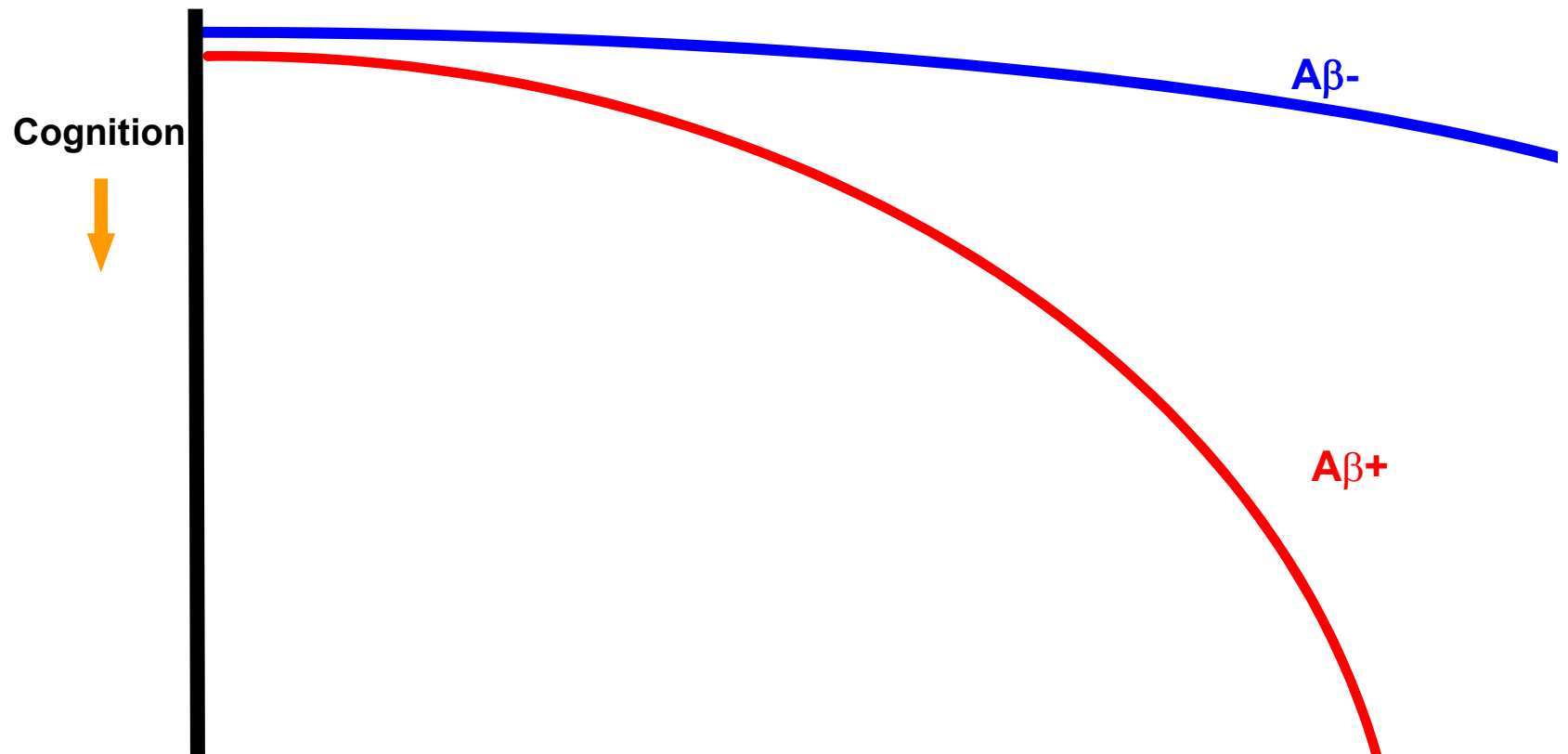
## Update on AD Secondary Prevention Trials

- Dominantly Inherited Alzheimer Network (DIAN)
  - PS-1, PS-2, APP – Solanezumab, Gantenerumab, (BACEi)
- Alzheimer Prevention Initiative (API)
  - PS-1 Colombian kindred – Crenezumab
  - APOE 4 Carriers – Active Vaccine, BACEi
- TOMMorrow Trial – TOMM40- Pioglitazone - Stopped
- Anti-Amyloid Treatment in Asymptomatic AD (A4)
  - A4 – A $\beta$ + normal 65-85yo– Solanezumab
  - EARLY (“A5”) A $\beta$ + normal 60-85yo–BACEi – Stopped
  - A3 – Subthreshold A $\beta$  >Age 50 (Coming soon)

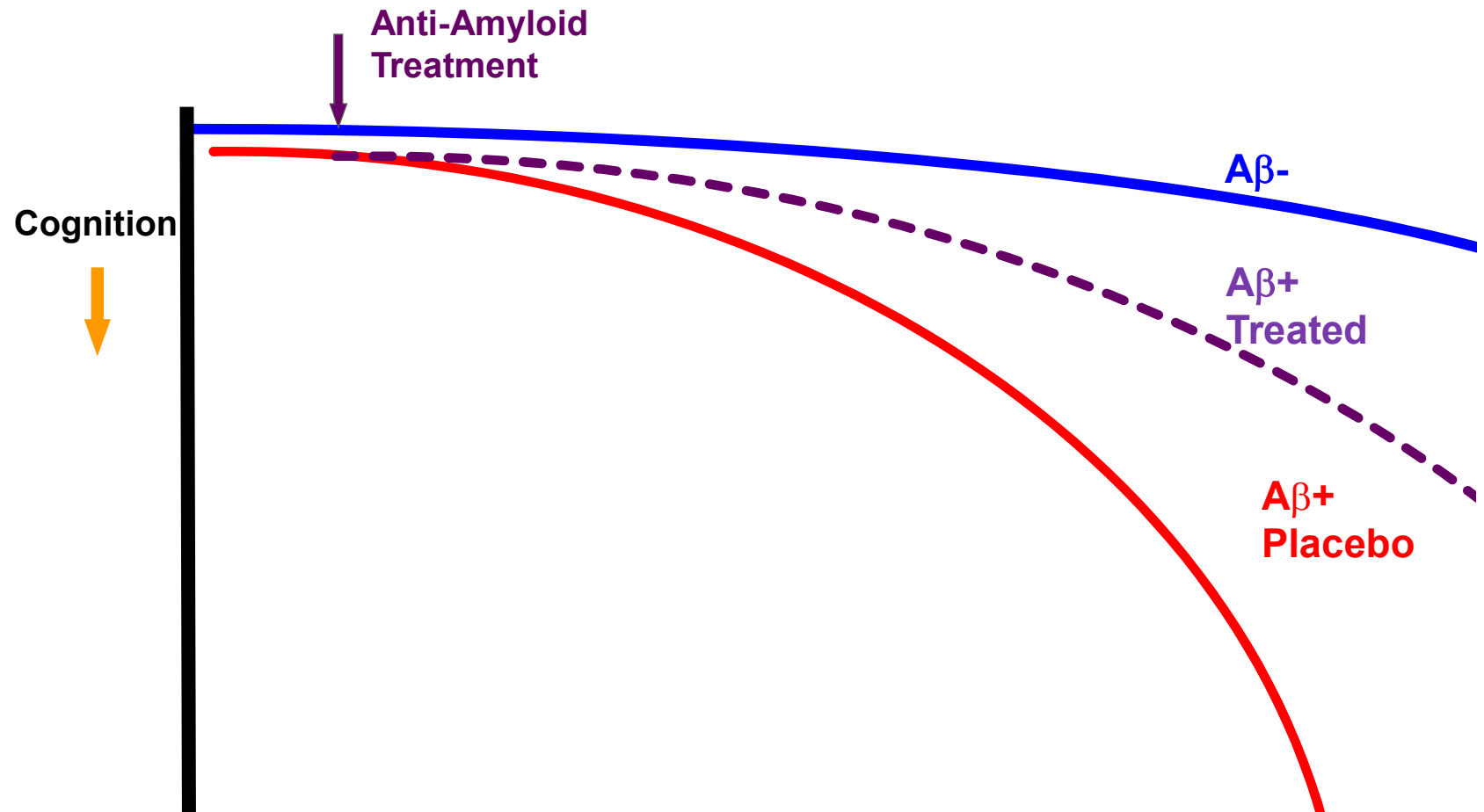
## Anti-Amyloid Treatment of Asymptomatic Alzheimer's disease (A4) Study

- Secondary prevention trial in clinically normal older individuals (age 65-85y) elevated A $\beta$  screening PET
- Phase 3 randomized, double-blind, placebo-controlled trial of solanezumab vs. placebo – 240 weeks (4.5 years)
- 67 sites in U.S., Canada, Australia, Japan
- Enrollment goal N=1150; 575 per treatment arm, stratified by APOE
- LEARN companion study of A $\beta$ –
- Amyloid Disclosure Ethics Substudy

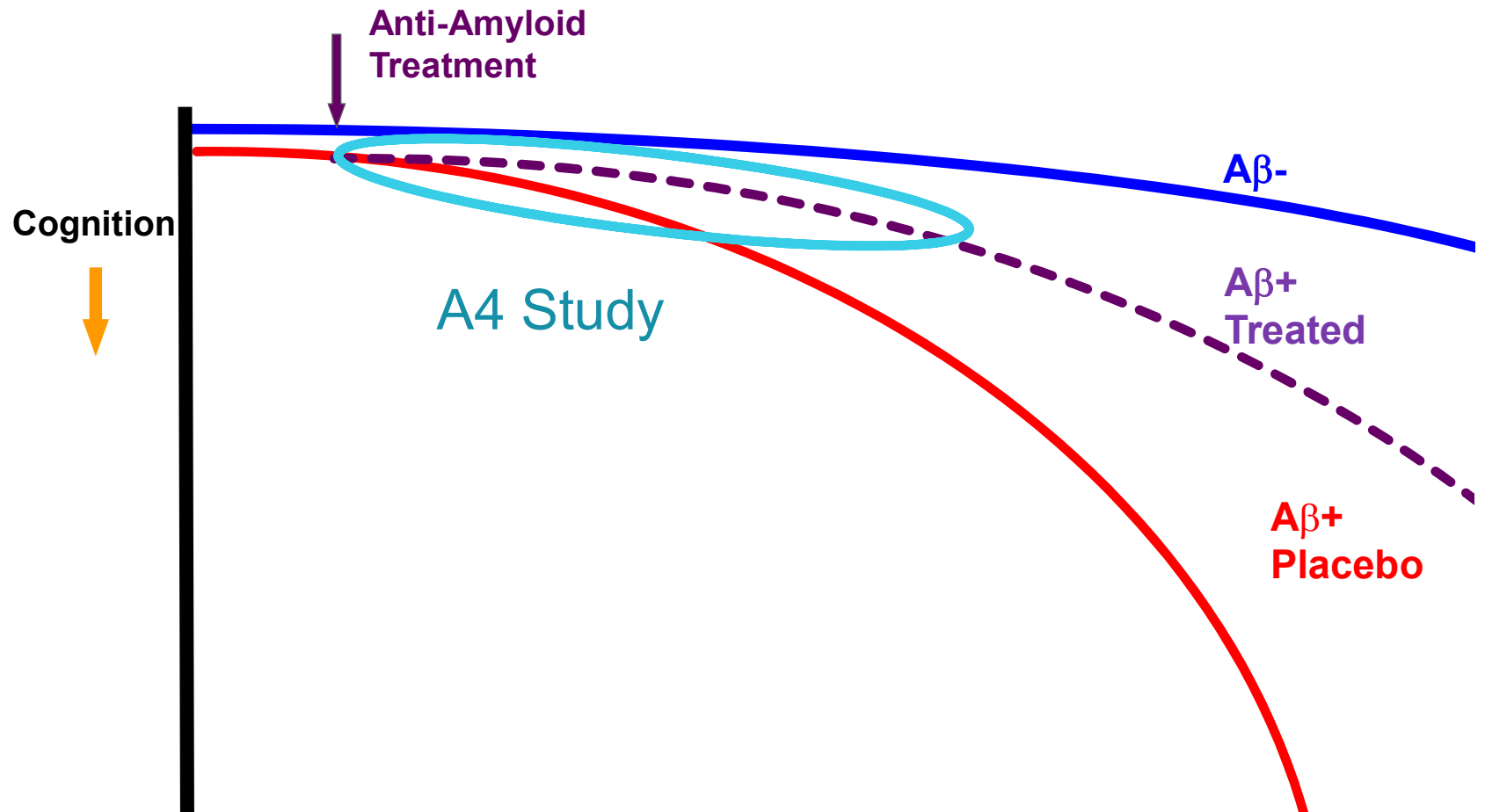
# Anti-Amyloid Treatment in Asymptomatic AD



# Anti-Amyloid Treatment in Asymptomatic AD



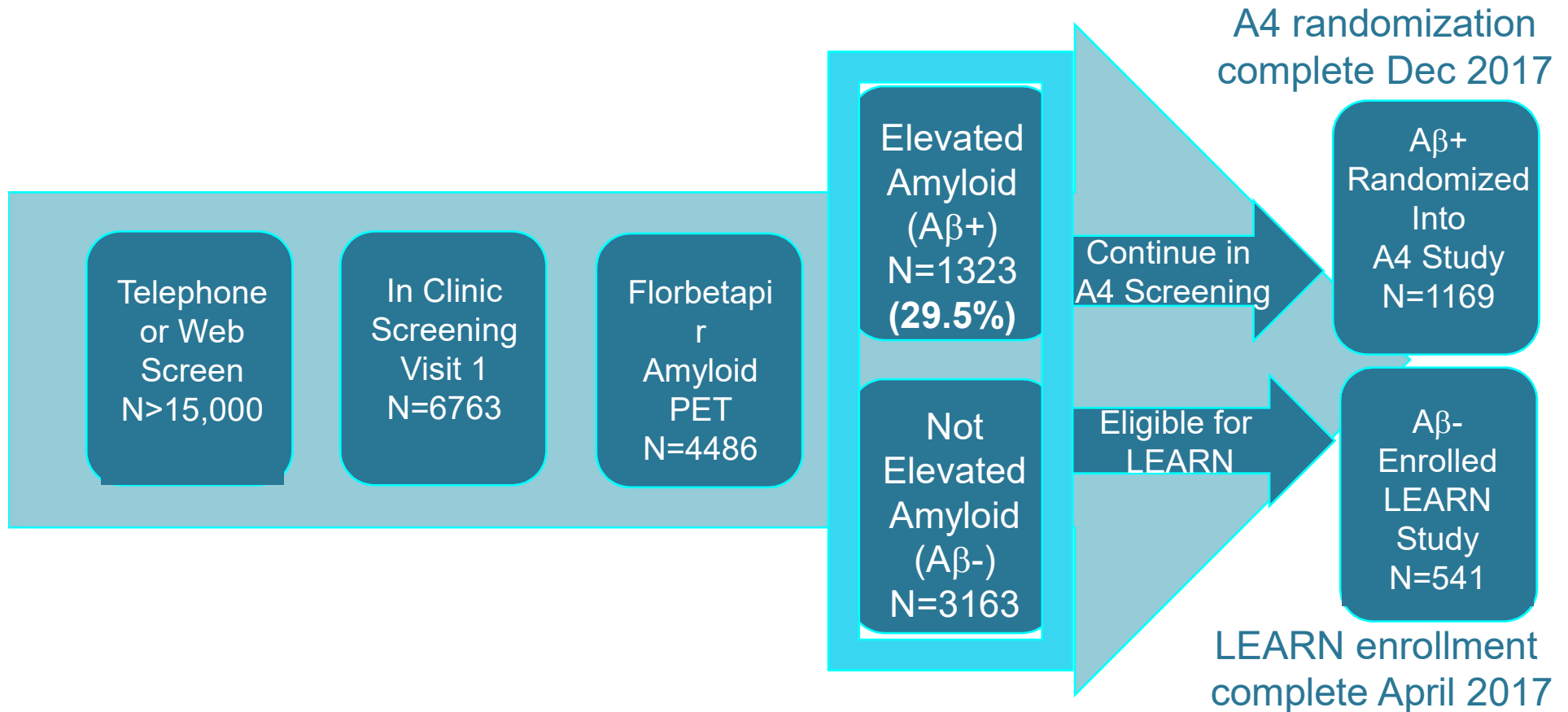
# Anti-Amyloid Treatment in Asymptomatic AD



## A4 Screening Process

- Scr Visit 1 – Cognitive, Functional, Medical
  - Eligible participants= CDR 0, MMSE 25-30, LM IIa 6-18
- Scr V2 - Eligible participants underwent Florbetapir Amyloid PET imaging
  - Amyloid eligibility algorithm - Elevated  $A\beta+$  SUVR  $>1.15$  and/or visual read positive if SUVR  $>1.10$
- Scr V3 - Amyloid disclosure visit
- Scr V4 – MRI
- Scr V5 – CSF or Tau PET (optional)

# Results: A4 Screening Results





## A4 PET Screening Demographics

	Not Elevated Amyloid (A $\beta$ -)	Elevated Amyloid (A $\beta$ +)	P-value A $\beta$ - vs A $\beta$ +
	<b><i>N</i> = 3163</b>	<b><i>N</i> = 1323</b>	
<b>Age</b> Mean years (S.D.)	71.0 (4.5)	72.1 (4.9)	<0.0001
<b>Education</b> Years (S.D.)	16.6 (2.9)	16.5 (2.8)	0.532
<b>Sex Female</b> (%)	60%	59%	0.641
<b>Marital Status</b> (%)			0.655
Married	70%	71%	
Divorced	14%	14%	
Widowed	10%	9%	
Never married	4%	4%	
<b>Retired</b>	76%	76%	0.927
<b>Amyloid PET SUVr</b>	<b>.99 (0.07)</b>	<b>1.33 (0.18)</b>	<b>&lt;0.0001</b>

## A4 Screening Demographics – Race/Ethnicity

	All Amyloid PET <i>N</i> =4486	Not Elevated (A $\beta$ -) <i>N</i> = 3163	Elevated (A $\beta$ +) <i>N</i> = 1323	P-value* A $\beta$ - vs A $\beta$ +
<b>All Minority</b>	503 (11%)	393 (12%)	110 (8%)	< 0.001
<b>Race</b>				
American Indian/Alaskan	32 (1%)	22 (1%)	10 (1%)	1.000
Asian	171 (4%)	141 (4%)	30 (2%)	0.002
Hawaiian/Pacific Islander	2 (0%)	2 (0%)	0 (0%)	1.000
Black/African American	167 (4%)	133 (4%)	34 (3%)	0.029
White	4116 (92%)	2866 (91%)	1250 (94%)	< 0.001
<b>Ethnicity</b>				
Hispanic/Latino	142 (3%)	103 (3%)	39 (3%)	0.641
Not Hispanic	4309 (96%)	3040 (96%)	1269 (96%)	0.801

\*p values not adjusted for multiple comparisons

## Results: Family History and APOE

Family History

**A $\beta$ - = 68%**

**A $\beta$ + = 74%**

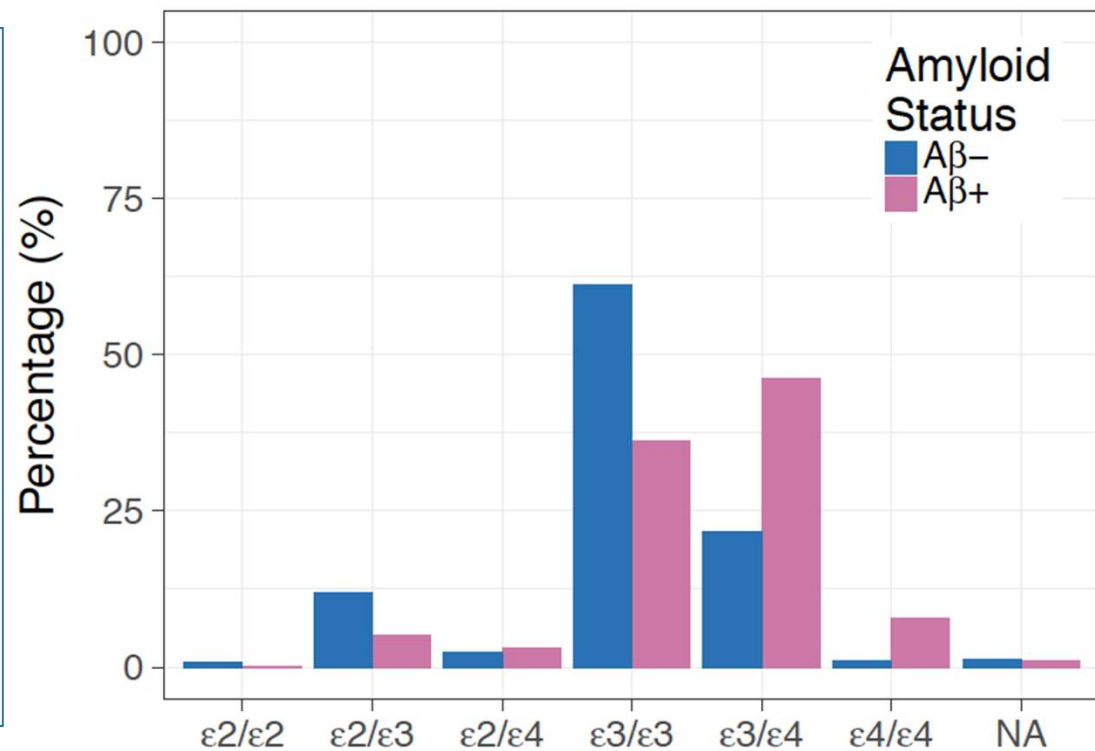
**p<0.001**

APOE  $\epsilon$ 4 Carrier

**A $\beta$ - = 25%**

**A $\beta$ + = 58%**

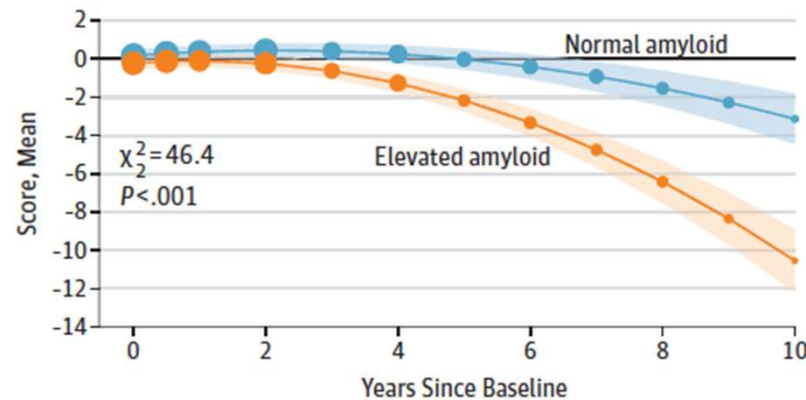
**p<0.0001**



# Preclinical Alzheimer Cognitive Composite

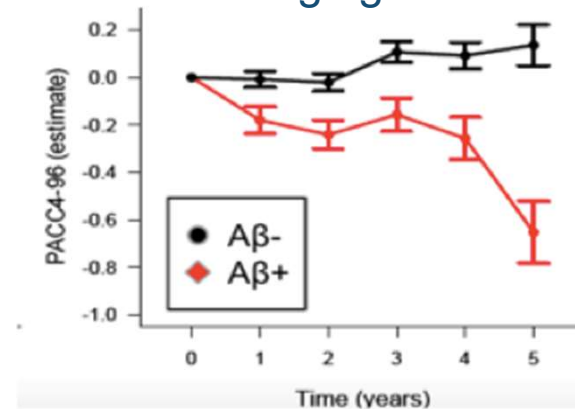
- PACC developed to track A $\beta$  related decline in CN

Alzheimer's Disease Neuroimaging Initiative



Donohue et al. *JAMA* 2017

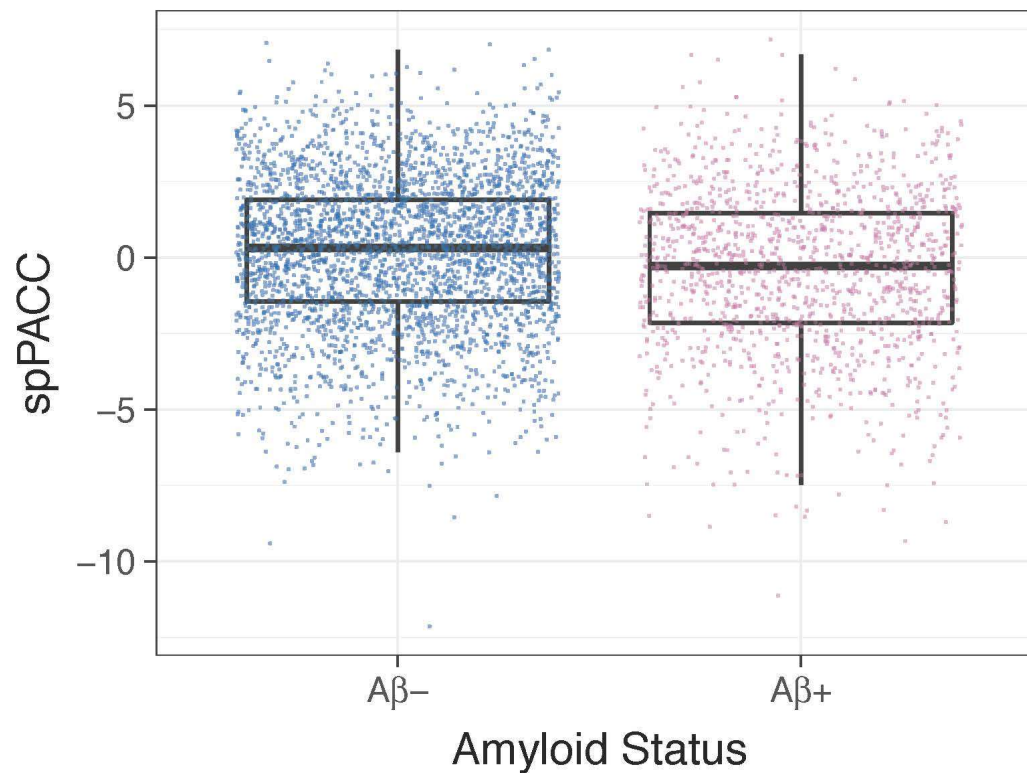
Harvard Aging Brain Study



Mormino et al *Alz & Dementia* 2017

- A4 PACC includes MMSE, Digit Symbol, LM Delayed Recall, FCSRT: Free plus Total score

# Results: A4 Screening PACC

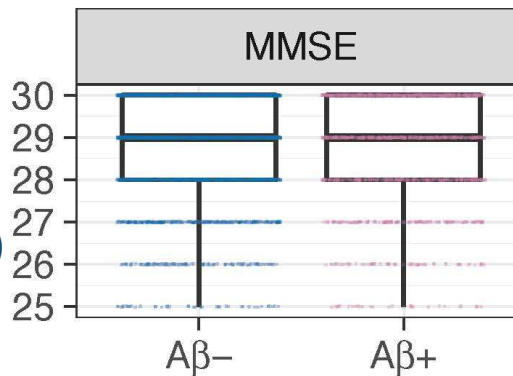


D=.32  
p<0.0001  
Adj\* p<0.0001

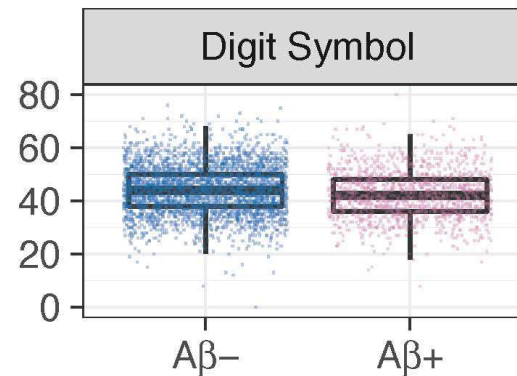
\*p value adjusted  
for age, gender,  
and education

# Results: PACC Components

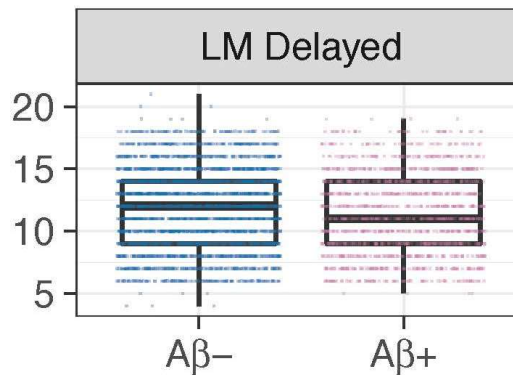
D= .11  
p=0.013  
Adj p=0.097 (ns)



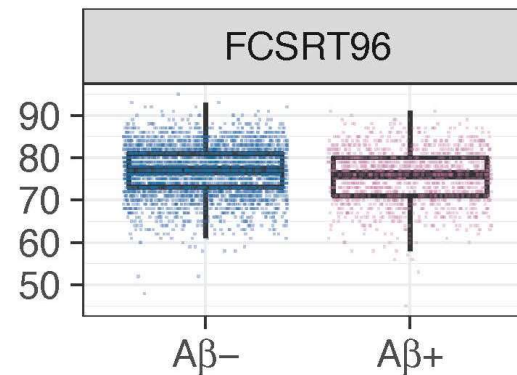
D= .26  
p<0.0001  
Adj p<0.0001



D= .17  
p=0.0002  
Adj p=0.0028



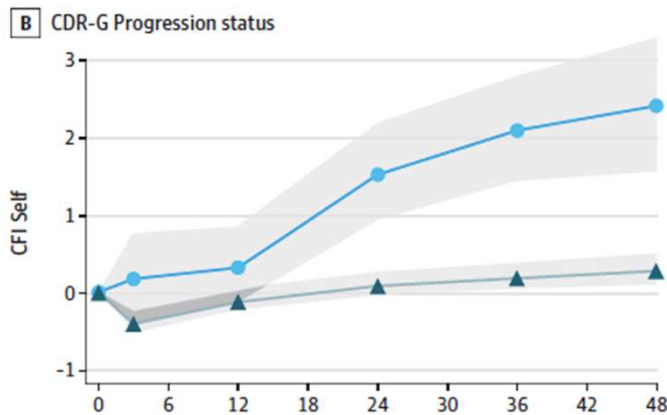
D= .27  
p<0.0001  
Adj p<0.0001



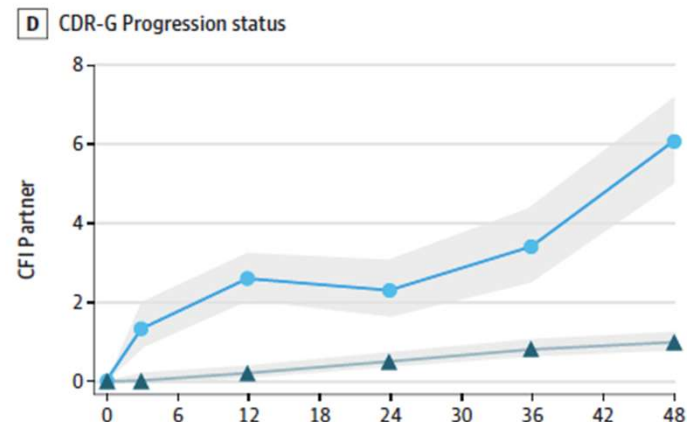
Amyloid Status

# Cognitive Function Index

- 15 item questionnaire - change in memory, change in ability to conduct high level activities *compared to 1 year ago*
- Completed by Participant and Study Partner

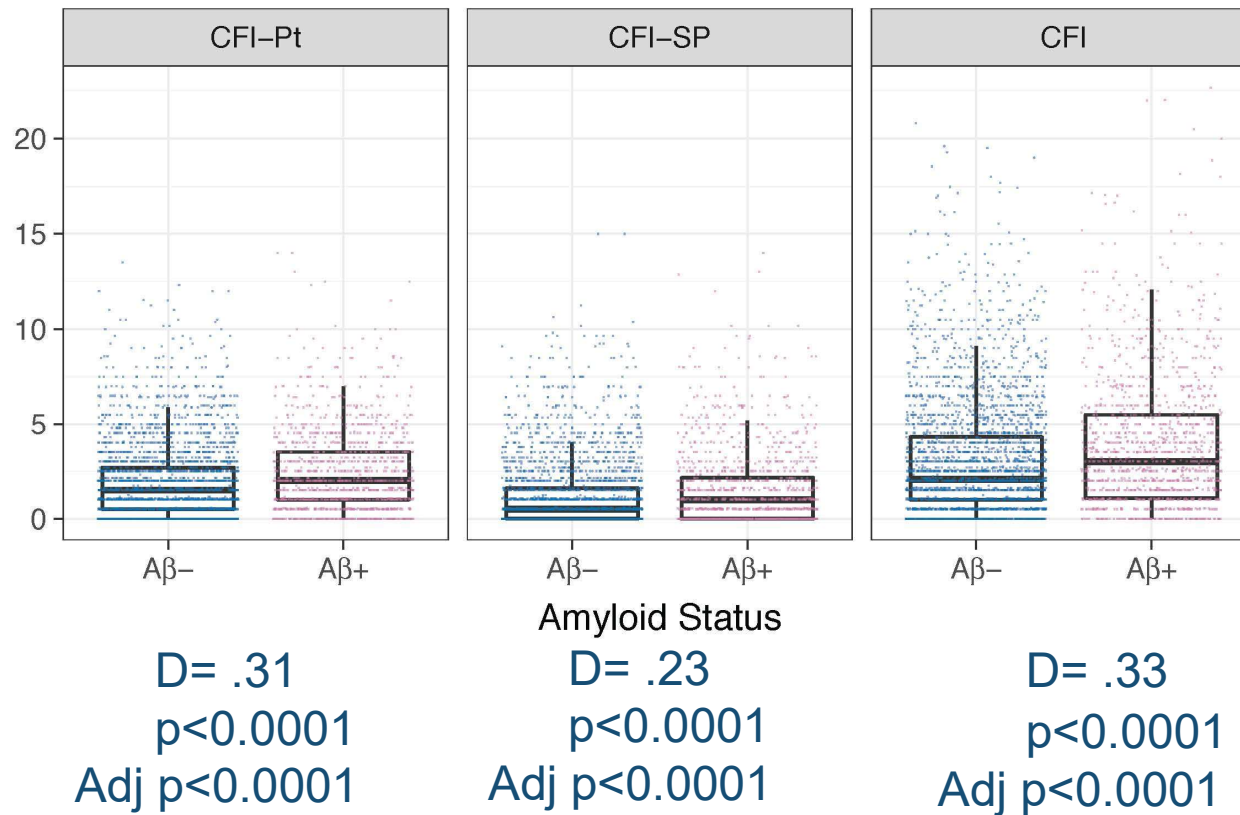


ADCS Prevention Instrument Study



Amariglio R et al *JAMA Neurology* 2015

# Results: A4 Screening CFI



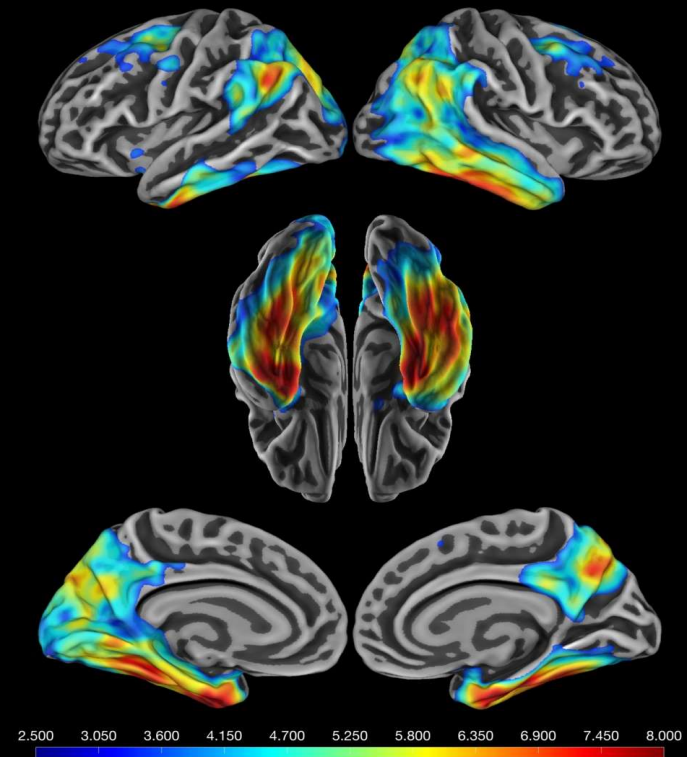
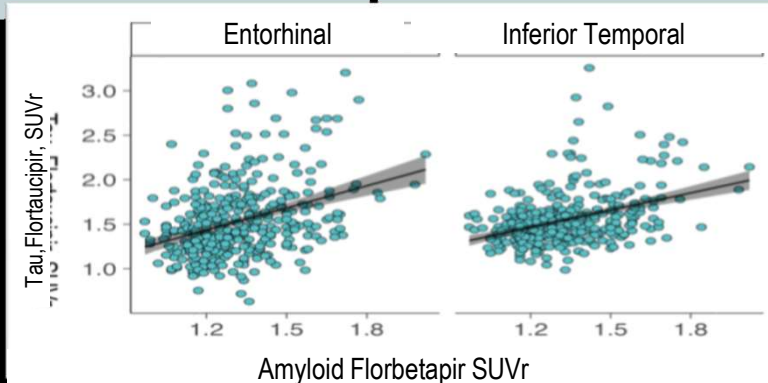


## A4 Longitudinal Biomarker Outcomes

- PET amyloid imaging – Baseline, 240 weeks
  - Decrease in mean cortical SUVR
- CSF phospho-tau and tau (in subset) – BL, 240
- Volumetric/Safety MRI – BL, 12, 84, 168, 240 weeks
  - Cortical thinning
  - Hippocampal atrophy
- Functional Connectivity MRI – BL, 12, 84, 168, 240 weeks
  - Task-free default network connectivity
- Tau PET imaging – BL, 84, 168, 240 weeks (Alz Assoc and AMP funding)

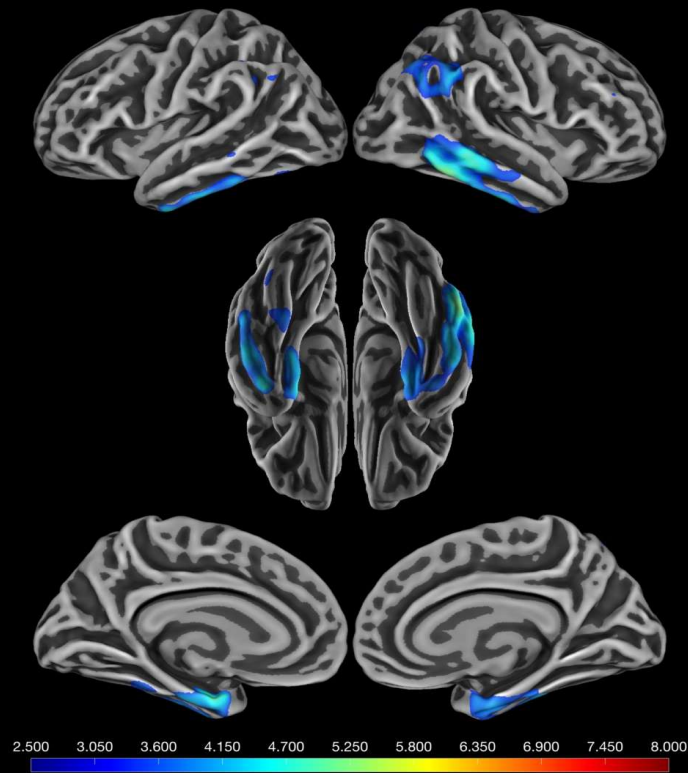
# A4 Study Baseline Tau PET

Demographics	Total (N = 390)
Age, y	72.1 (4.8)* Range: [65.0, 85.5]
Sex (n females. %)	224 F (57.4%)
Education, y	16.16 (2.8) Range: [8, 30]
PACC Score	-0.60 (2.76) Range: [-11.11, 6.67]
Amyloid PET Global Burden, SUVR	1.317 (0.18) Range: [.97, 2.02]
Tau PET Entorhinal (EC), SUVR	1.531 (0.41) Range: [0.63, 3.20]
Tau PET Inferior Temporal (IT), SUVR	1.540 (0.29) Range: [0.99, 3.26]

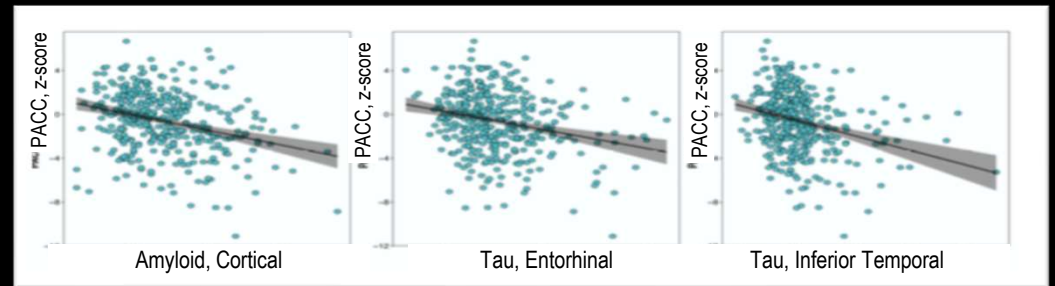


Johnson K et al AAIC 2018

# Baseline A4 Tau PET and Cognitive Performance



		Amyloid	Tau
P A C C	EC	$\beta = -0.18$ [-0.27, -0.09] $p < 0.001$	$\beta = -0.17$ [-0.26, -0.08] $p < 0.001$
	IT	$\beta = -0.17$ [-0.26, -0.07] $p < 0.001$	$\beta = -0.19$ [-0.28, -0.09] $p < 0.001$



Johnson K et al AAIC 2018

# A4 Study Screening Conclusions

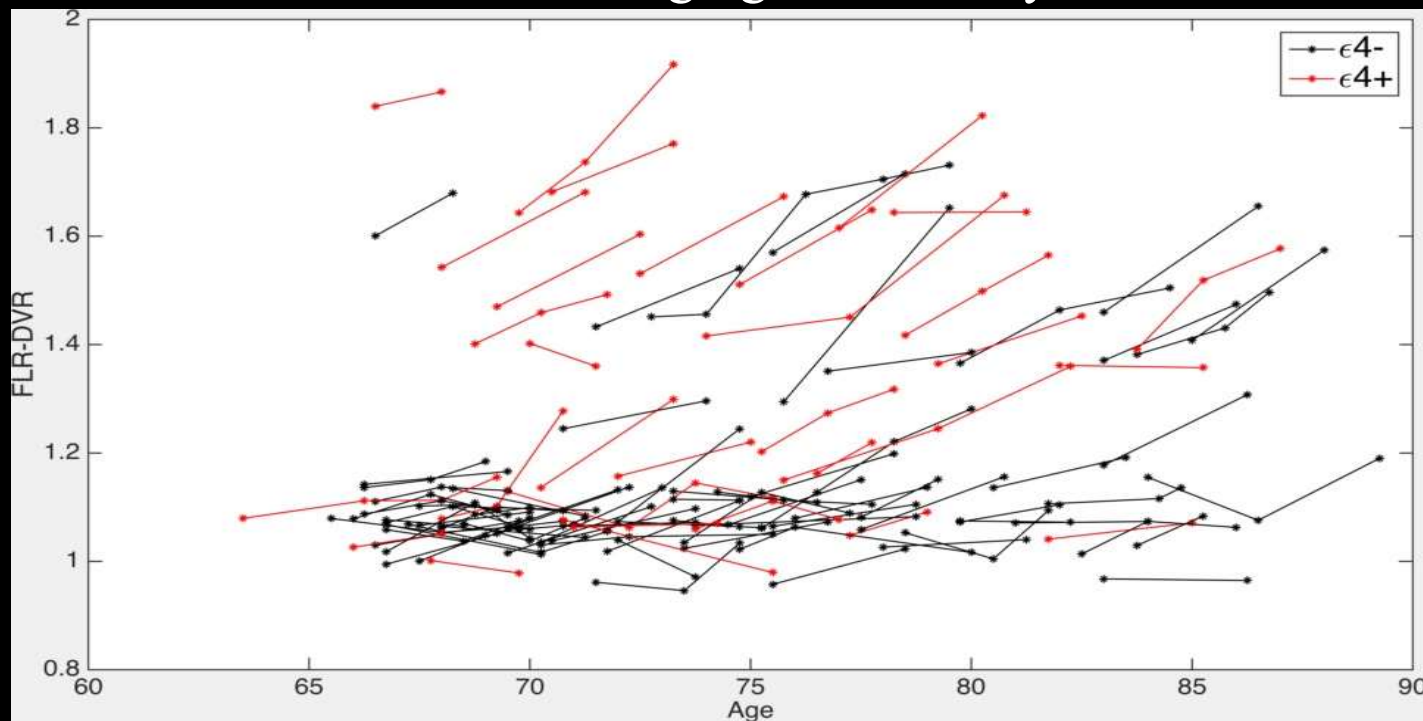
- Eligible A $\beta$ + participants show similar demographic characteristics to patients in AD dementia trials
- A $\beta$ + CN performed less well on screening cognitive tests and reported higher concerns about recent change in cognitive function
- Higher levels of A $\beta$  associated with higher levels of Tau, even among group of all A $\beta$ + cognitively normal older individuals
- Feasible to enroll prevention trials in participants at high risk for progression to sporadic AD dementia
- A4 is well positioned to test whether decreasing A $\beta$  can slow cognitive decline in preclinical AD
- Have to wait for answers in 2022!

## Moving Even Earlier in the Alzheimer's Continuum

- A $\beta$  begins to accumulate two decades prior to dementia, and once A $\beta$  accumulation begins, there is no going back
- Detectable subtle cognitive decline associated with subthreshold A $\beta$  and tau accumulation
- More than half of the “A $\beta$  positive” normals already have abnormal levels of tau pathology
- Once both A $\beta$  and tau markers are clearly elevated, very high risk for imminent cognitive decline
- Why would we wait for that stage of disease to intervene?

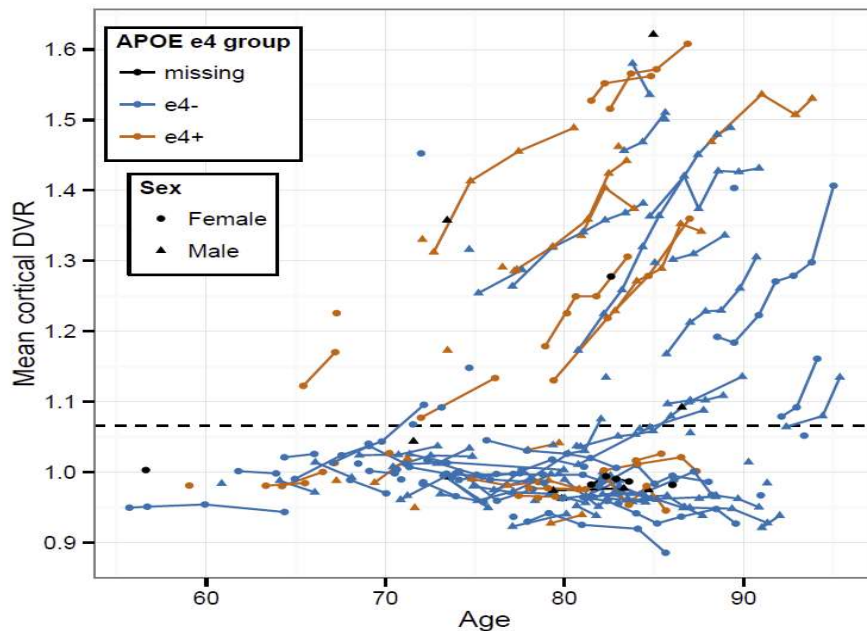
# Longitudinal Amyloid- $\beta$ Accumulation in Clinically Normal Elders

Harvard Aging Brain Study

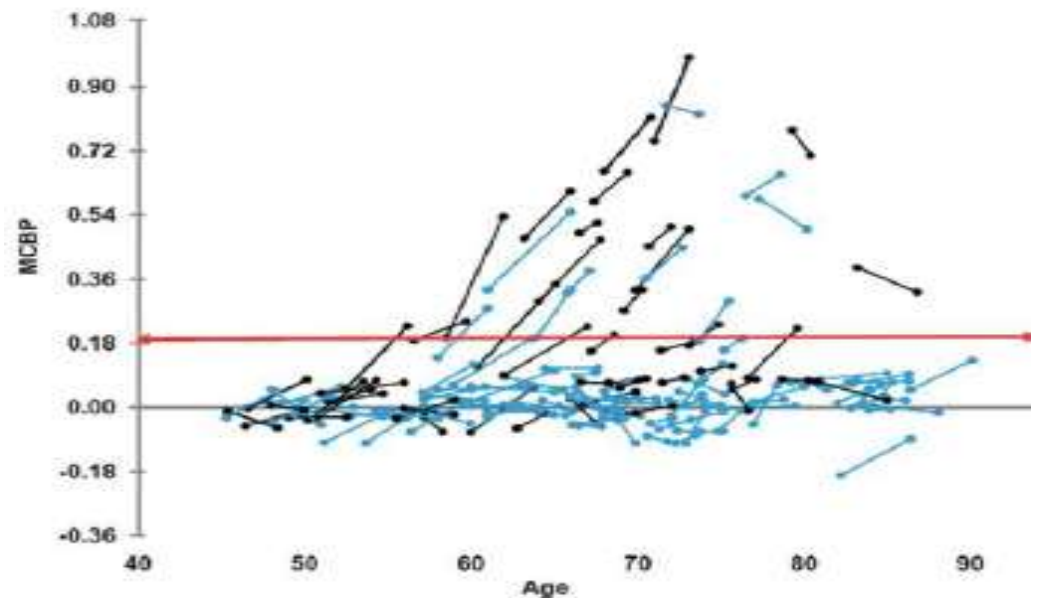


Aaron Schultz and Keith Johnson HAI 2015

# Longitudinal Amyloid- $\beta$ Accumulation in Clinically Normal Elders



Bilgel et al. *Alz & Dementia* 2016



Vlassenko et al. *Ann Neurol* 2011

## A4 Study - Anti-Amyloid Treatment in Asymptomatic AD

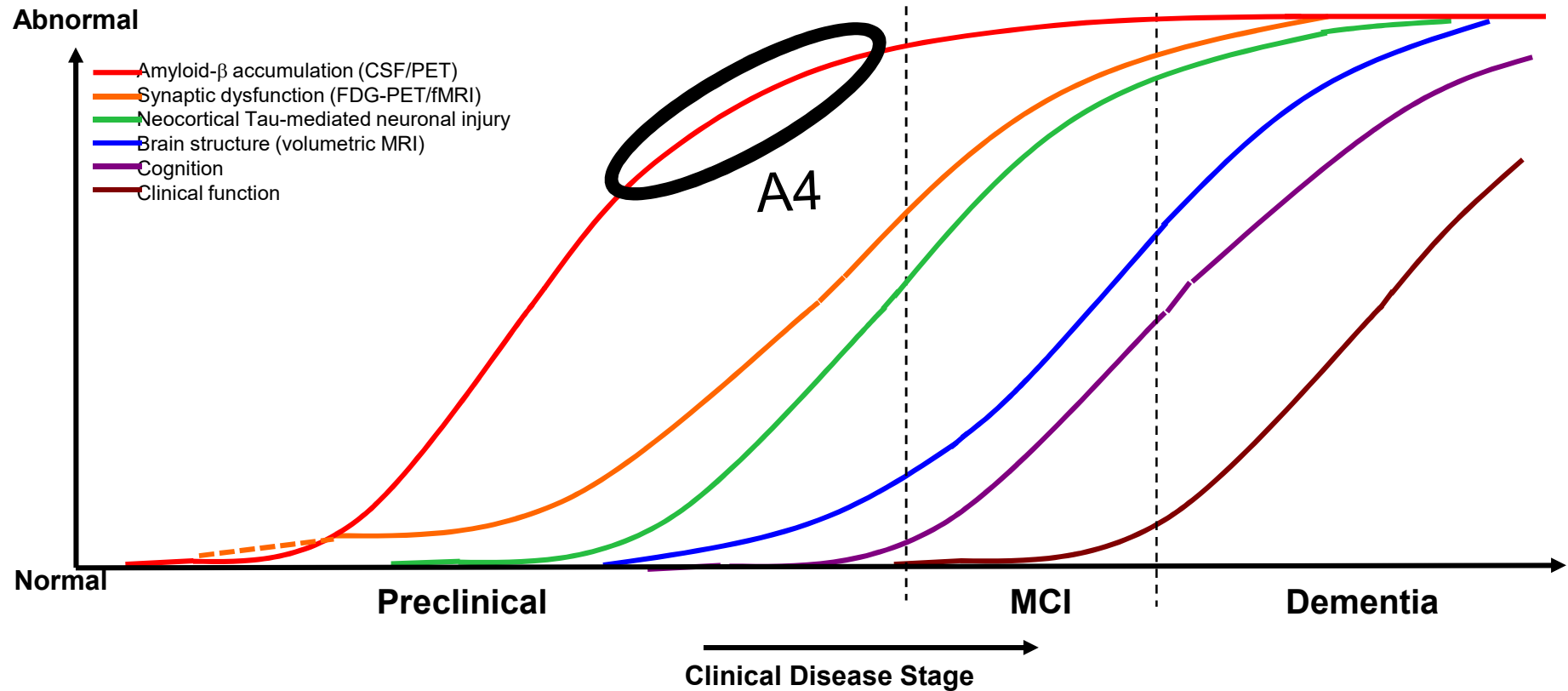
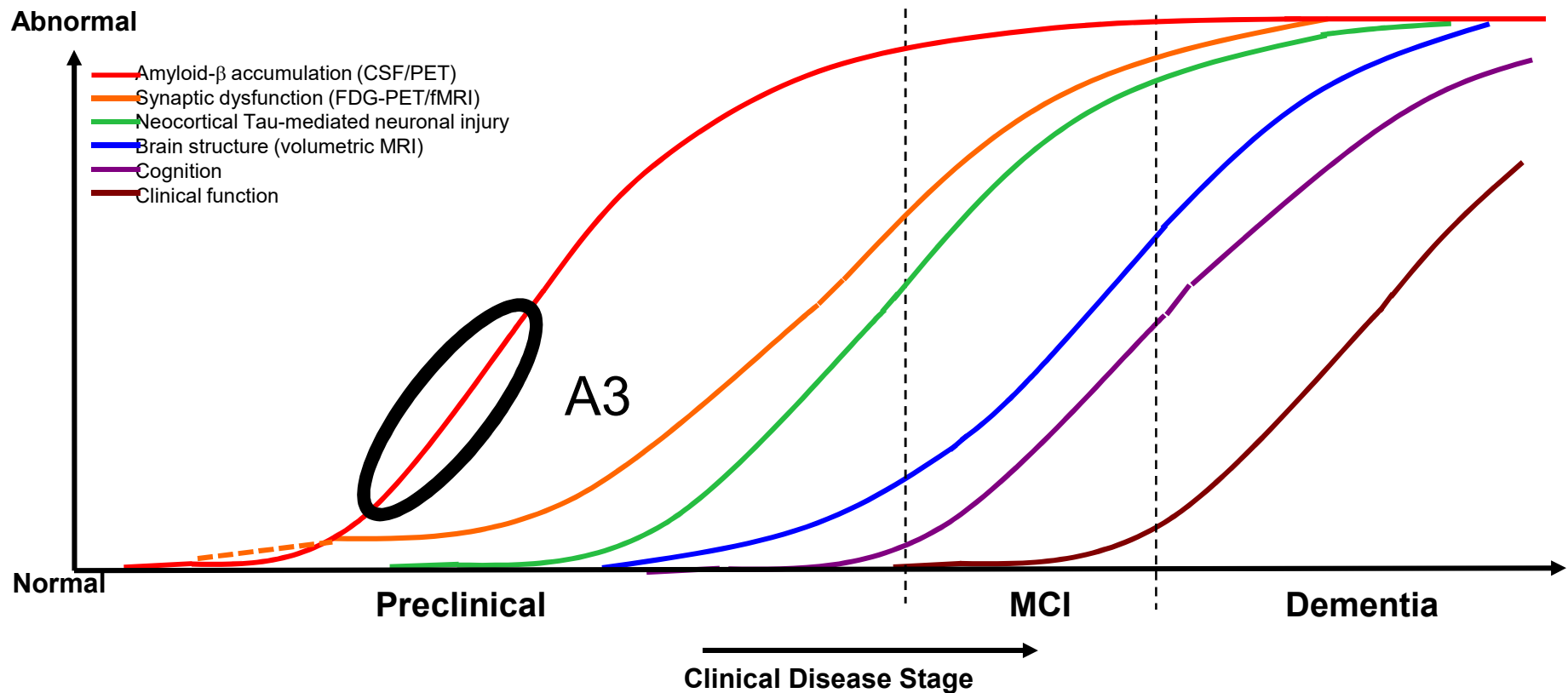


Figure adapted from Jack *et al.* 2010, Sperling *et al.* 2011



## A3 Study = Ante-Amyloid prevention of AD Getting closer to Primary Prevention!



## A3 Study

- A3 will utilize an Age x APOE x SUVR algorithm, leverage A4 and other trial “screen-fails” to identify “subthreshold” A $\beta$  at high risk for accumulation
- Four year Phase IIb trial
- Primary outcomes are biomarkers – rate of A $\beta$  accumulation, tau PET spreading, MRI atrophy
- Exploratory sensitive cognitive outcomes (iPAD)
- Public-private-philanthropic partnership
- Still making decisions about best therapeutic options given recent data on BACEi, vaccines, antibodies, etc.

## New Prevention Initiatives

- Combination prevention trial – “A45”
  - Induction treatment with plaque clearing antibody followed by maintenance therapy aimed at preventing reaccumulation
- TRC-PAD: Trial Ready Cohorts for Preclinical/Prodromal AD
  - Improve efficiency of screening for prevention trials
  - Develop algorithm to reliably predict A $\beta$ + using age, APOE, family history, digital cognitive testing, self-report of function
  - Will incorporate plasma A $\beta$  biomarkers
- Primary prevention trials
  - DIAN Primary Prevention , someday sporadic AD “A2”...

# Encouraging history from other fields

- Cholesterol Wars in Cardiology
  - Role of cholesterol very controversial until field developed reliable measurements for cholesterol
  - Secondary prevention trials in familial hypercholesterolemia and in post-myocardial infarction
  - Reduction of cholesterol estimated to have reduced cardiac morbidity and mortality by 28%
  - As in “A3” rationale, recommendations for treating cholesterol have steadily evolved to lower LDL
- We MUST be steadfast in our mission to fully test the amyloid hypothesis and prevent AD!

# Acknowledgments

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